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Development of new covid-19 vaccines from india : A systematic review

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ABSTRACT

Extreme acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is an extremely pathogenic new virus that has triggered the current worldwide coronavirus disease pandemic (COVID-19). Currently, substantial effort has been made to produce successful and safe medicines and SARS-CoV-2 vaccines. To avoid more morbidity and death, a successful vaccine is important. Though some regions which deploy COVID-19 vaccines on the basis of protection and immunogenicity data alone, the aim of vaccine research is to obtain direct proof of vaccine effectiveness in protecting humans against SARS-CoV-2 and COVID-19 infections in order to selectively increase the production of effective vaccines. A SARS-CoV-2 candidate vaccine can function against infection, illness, or transmission and a vaccine that is capable of minimising all of these components may lead to disease control. In this study, we discussed the Bharat Biotech and Covishield Serum Institute of India's Covaxin - India's First Indigenous Covid-19 Vaccine.

Keywords: Covaxin, Covishield, SARS-CoV-2, COVID-19, Serum Institute, Bharat Biotech.

INTRODUCTION

According to the WHO, multiple cases of pneumonia of unknown aetiology were found in the city of Wuhan in central China in December 2019. In Wuhan, China, patients who had viral pneumonia due to an unknown microbial agent were documented at the end of December 2019. A novel coronavirus, provisionally named the 2019 novel coronavirus (2019-nCoV), was subsequently identified as the causative pathogen. The quickly circulating coronavirus disease was declared by WHO on February 11th 2020 as COVID-19. More than 2000 incidents of COVID-19 infection have been confirmed as of 26 January 2020, most of which included individuals living in or visiting Wuhan, and human-to-human transmission has been confirmed [1].

Most of the initial affected individuals is associated with exposure to the seafood industry [2]. In 2020, 2835 confirmed cases were reported by the Chinese authorities in mainland China, including 81 deaths. Furthermore, in Hong Kong, Macao and Taiwan, 19 confirmed cases were reported and 39 imported cases were identified in Thailand, Japan, South Korea, the United States, Vietnam, Singapore, Nepal, France, Australia and

Canada. COVID-19, which is closely linked to extreme acute respiratory syndrome CoV (SARS-CoV), was quickly identified as the pathogen [3].

A novel coronavirus, 2019-n CoV, as the causative agent, has officially been announced by the Chinese authorities [4, 5]. Coronaviruses (CoV) are a family of viruses called Coronaviridae. There are three genera in the subfamily Coronavirinae: alphacoronavirus, betacoronavirus, and gamma-coronavirus. Two genera, torovirus and bafinivirus, are in the subfamily Torovirinae. CoV can lead to a number of symptoms as mild as common cold, fever and cough, and as severe as pneumonia, kidney failure or even death in respiratory distress [6]. These viruses are zoonotic, that is, spread between animals and humans. A few coronaviruses were previously recognised: MERS-CoV, which causes respiratory syndrome in the Middle East and was transmitted to humans from dromedary camels, and SARS-CoV, which causes extreme acute respiratory syndrome and was transmitted to humans from civet cats [7, 8]. In a wet market in Wuhan where game animals and beef were sold, COVID-19 is believed to have been zoonotically transmitted [9].

Popular human coronaviruses, such as types 229E, NL63, OC43 and HKU1, however, cause mild to severe symptoms of the upper respiratory tract, sore throat, runny nose and cough. Other symptoms are fever, headache, and feeling unwell in general. In people with cardiopulmonary disorders, immuno compromised patients, children, and older adults, more serious conditions affecting the lower respiratory tract, such as pneumonia and bronchitis, are more frequent. Via coughing or sneezing or near physical contact such as rubbing or shaking hands, these viruses are transferred from infected humans to others through air [10].

A total of 94,962,048 confirmed cases in the country, spread in 81 countries, resulting in the epidemic of COVID-19, of which 2,031,142 died. Of the total cases, the United States of America has the highest number, with 24,306,043 cases, followed by 10,558,710 in India, 8,456,705 in Brazil, 3,544,623 in Russia, 3,357,361 in the United Kingdom, 2,894,347 in France, etc [11]. His study article deals with the Covid-19 preventive vaccine manufactured in India.

COVAXIN

BBV152 (also known as Covaxin) is a COVID-19 inactivated virus-based vaccine developed in partnership with the Indian Council of Medical Research by Bharat Biotech. Covaxin, India's first indigenous COVID-19 vaccine, is the first indigenous COVID-19 vaccine developed by Bharat Biotech in partnership with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, inactivated vaccine is produced and processed in the high containment facility of Bharat Biotech's BSL-3 (Bio-Safety Level 3). The vaccine earned DCGI clearance for Phase I & II Human Clinical Trials, and studies started in July 2020 across India. Bharat Biotech obtained DCGI clearance for Phase 3 clinical trials in 26,000 participants in over 25 centres across India after successful completion of the interim review of the Phase 1 & 2 clinical trials of Covaxin [12, 13].

The National Institute of Virology of the Indian Council of Medical Research (ICMR) accepted and supplied the virus strains in May 2020 for the production of a fully indigenous COVID-19 vaccine.[14, 15] In June 2020, the company was approved by the Drugs Controller General of India (DCGI), Government of India, to perform Phase 1 and Phase 2 human trials of a developmental COVID-19 vaccine called Covaxin.[16] A total of 12 sites were chosen by the Indian Council for Medical Research for Phase I and II randomised, double-blind and placebo-controlled vaccine candidate clinical trials.[17, 18] The company announced the study for Phase I trials in December 2020 and presented the findings via medRxiv preprint.[20-22]

In November 2020, after completion of Phase I and II, Covaxin was authorised to perform Phase III clinical trials[23, 24] The study involves a randomised, double-blinded, placebo-controlled study among volunteers aged 18 and above and began [25] Approximately 26,000 volunteers from across India will be involved in the Phase III trials.[26] The phase III trials will cover a total of 26,000 volunteers from across India [27] The rejection rate for Phase III trials was far higher than for Phase I and Phase II trials. As a result, by 22 December, only 13,000 volunteers were employed, with the figure rising to 23,000 by 5 January [28-30]

On its vero cell manufacturing platform [31] that has the potential to deliver around 300 million doses, Bharat Biotech produces the vaccine candidate through at-risk manufacturing [32] The company is in the process of setting up a second plant to make Covaxin at its Genome Valley facility in Hyderabad. For another place in the country to produce the vaccine, the company is in talks with other state governments including Odisha [33]. Besides this, global tie-ups for the development of Covaxin are also being explored.[34] In December 2020, OcugenInc entered into a collaboration with Bharat Biotech to co-develop Covaxin for the U.S. market.[35, 36]. In January 2021, Precisa Med entered into an arrangement to supply Covaxin in Brazil with Bharat Biotech [37]

Bharat Biotech applied for an emergency use authorization (EUA) from the Drugs Controller General of India (DCGI), Government of India.[38] After Serum Institute of India and Pfizer, it was the third company to apply for emergency use approval.[39]. On 2 January 2021, an EUA permit was recommended by the Central Drugs Quality Control Organisation (CDSCO) [40], which was issued on 3 January.[41] The emergency approval was given prior to the release of Phase III trial results. In certain parts of the newspapers, this has been criticised [42].

Restricted emergency approval of the Covaxin, Covid-19 vaccine, developed by Bharat Biotech in partnership with ICMR and NIV, was issued on 3 January 2020, a decision challenged by domain experts. Here's a look at the way vaccines are approved by India. With some experts challenging the government's decision, the limited emergency approval granted to a Covid-19 vaccine produced by Bharat Biotech on January 3, 2020 created a major furore. Bharat Biotech, in cooperation with the Indian Council for Medical Research (ICMR) and the National Institute of Virology (NIV), Pune, has obtained permission for its vaccine, Covaxin—a Whole Vision Inactivated Corona Virus Vaccine. The approval was limited and conditional upon the declaration by Union Health Minister Harsh Vardhan that those getting Covaxin shots would be tracked in the same manner as those in clinical trials for volunteers. A variety of domain experts expressed concern at the decision that the data relating to Covaxin clinical trials had not been made public.

The DCGI released a statement on January 3, 2020, noting that Covaxin was "developed on Vero cell platform, which has well established track record of safety and efficacy in the country and globally" The DCGI said that Bharat Biotech, maker of Covaxin, shared its "safety and immunogenicity data" from its animal studies, including "challenge studies on non-human primates (Rhesus macaques) and hamsters" with the CSDSCO drug regulator. The DCGI has shown "demonstrated that the vaccine is safe and provides a robust immune response" in phase I and phase II with respect to clinical human trials. The drug regulator said, citing phase III results from around 22,500 patients, "The vaccine has been found to be safe as per the data available till date." The CSDSCO's Topic Expert Committee (SEC) checked the Covaxin safety and immunogenicity data, the DCGI said, before recommending authorization for restricted use of this Covid-19 vaccine in emergency circumstances [13].

In the past, there have been many examples where the Indian drug regulator issued emergency permission based solely on evidence on immunogenicity. H1N1 vaccines were all approved on the basis of phase 2 immunogenicity data by the Serum Institute of India, Bharat Biotech and ZydusCadila. Immunogenicity refers to the vaccine's ability to elicit a reaction from the antibody and T-Cell. Notification of CDSCO recommendations for drug and vaccine approval in the 2019 gazette which provides for emergency approval based on Phase 2 results if the vaccine is on a proven and developed framework and if strong immunogenicity data are seen in Phase 2 trials. The vaccine is based on a virion-inactivated platform (where the generating ability of the SARS CoV-2 virus is inactivated) and is developed using well proven Vero cell technology. Bharat Biotech CMD has reported that it has phase 3 safety data, 1,000-person immunogenicity data, as well as preclinical animal data. Ella said that in tests, the vaccine showed fewer than 10 percent of side effects [43].

On 16 November, Phase 3 trials began. On Sunday, the government's press release reported that 25,800 volunteers had started Phase 3 trials, of which 22,500 had received the first dose. Covaxin is injected twice, with a gap of 27 days, intramuscularly. Next month, the interim safety data is expected. The ability of Covaxin to create resistance to the new mutant strain was a crucial

factor in the granting of emergency clearance. "It is present in 34 countries right now. Some of the vaccines are only aimed at the virus spike protein, and they may not be successful. We are looking at a whole virus vaccine (Covaxin) from that point of view, which could theoretically have advantages,' he added. DrGuleria acknowledged, however, that more laboratory research on Covaxin providing some security against the latest UK variant is needed at this stage. An inactivated virus is used by Bharat Biotech, using the platform deployed in other vaccines in our region. The proof that is being put forward is that the antibody response could be more robust to take care of any mutation when the whole virus is being used as the antigen [44].

COVISHIELD

Covishield, known as the Oxford-AstraZeneca vaccine, is a COVID-19 vaccine developed by Oxford University and AstraZeneca by intramuscular injection, using the adapted chimpanzee adenovirus ChAdOx1 as a vector.[45] When a half-dose was followed by a full-dose after at least one month, one dosing regimen showed 90 percent effectiveness.[46] Another dosing regimen showed 6 Sarah Gilbert, Adrian Hill, Andrew Pollard, Teresa Lambe, Sandy Douglas and Catherine Green are responsible for the squad [47]. As of December 2020, Phase III clinical testing is ongoing on the vaccine candidate [48]. The vaccine was approved for use in the UK vaccination programme, and the first vaccination was administered [50].

A replication-deficient simian adenovirus vector is the AZD1222 vaccine, carrying the full-length codon-optimized coding sequence of SARS-CoV-2 spike protein along with a leading sequence of tissue plasminogen activator (tPA) [51]. The SARS-CoV-2 genome sequenced in Wuhan was used by the researchers. It is not necessary to replicate the modified chimpanzee adenovirus, but it does not cause further infection and only serves as a vector to transfer the SARS-CoV-2 spike protein [52]. The spike S1 protein is an external protein that helps the coronavirus type SARS to reach cells via the ACE2 enzymatic domain [53]. This spike protein is released after vaccination, promoting the immune system to attack the coronavirus if it later infects the body [54].

The Jenner Institute decided in February 2020 to partner with the Italian company Advent Srl to create the first batch of vaccine candidates for clinical trials [55]. The US National Institute of Allergy and Infectious Diseases (NIAID) reported in June 2020 that the third phase of prospective vaccine research produced by Oxford University and AstraZeneca will commence in July 2020 [58]. AstraZeneca declared a global halt to the vaccine study on 8 September 2020 while a potential allergic reaction was examined in a researcher in the United Kingdom [59]. After authorities determined that it was appropriate to do so, AstraZeneca and the University of Oxford resumed clinical trials in the United Kingdom on 13 September [60]. AstraZeneca was blamed for vaccine safety after expex concerns [61]. Although the trial resumed in the United Kingdom, Brazil, South Africa, Japan [62] and India, it remained on hold in the US until 23 October 2020 [63]. While, according to HHS Secretary Alex AzarAzar, the FDA investigated a patient disease that caused the clinical hold [64].

Dr. João Pedro R. Feitosa, a 28-year-old physician from Rio de Janeiro, Brazil, who obtained placebo instead of the research vaccine in a clinical trial of AZD1222, died from complications of COVID-19 on 15 October 2020 [65]. Anvisa, the Brazilian health department, confirmed that the study would proceed in Brazil [66]. Oxford University and AstraZeneca announced preliminary findings from the continuing phase 3 trials of the vaccine [67]. The approaches used in the report were questioned, combining results of 62 percent and 90 percent from various groups of test subjects offered different dosages of different dosages [68]. AstraZeneca said it would perform another multi-country study using the lower dose that culminated in a 90% claim [69]. These reports explained the full release of these preliminary findings from four ongoing, blinded, randomised, controlled trials on 8 December 2020 [70]. In the population that got the first dose of active vaccine more than 21 days earlier, no hospitalizations were reported. Significant adverse effects were balanced in the trials between the active and control arms, i.e. extra serious adverse events were not known to be triggered by the active vaccine. A case of transverse myelitis was identified as potentially due to vaccination 14 days after booster vaccination,

with an independent neurological committee finding idiopathic, short-segment, spinal cord demyelination as the most likely diagnosis. The remaining two cases of transverse myelitis were found unrelated to the injection, one in the vaccine community and the other in the control group [70].

AstraZeneca announced on 11 December 2020 that it will be investigating with the Russian Gamaleya Research Institute if their two adenovirus-based vaccines, AZD1222 and Gam-COVID-Vac, could be merged to provide increased standards of safety. "In Russia, clinical trials are scheduled to launch by the end of 2020 [71]. On 27 December 2020, Pascal Soriot, chief executive of AstraZeneca, said he claimed that researchers had developed a "winning recipe" in the shape of the COVID-19 Oxford-AstraZeneca vaccine, where two doses were used [72]. On 4 January 2021, Brian Pinker, 82, became the first person outside of clinical trials to receive the Oxford-AstraZeneca Covid-19 vaccine.

On 27 November 2020, the Government of the United Kingdom requested the Medicines and Healthcare Products Regulatory Agency to evaluate the temporary supply of the AZD1222 vaccine [73], and it was approved for use on 30 December 2020 as the second vaccine to enter the national roll-out [74]. On 29 December, Noel Wathion, Deputy Executive Director of the European Medicines Agency (EMA), announced that the EU regulatory authority would implement the vaccine. In an interview, he said, "They have not even filed an application with us yet"[75]. In January 2021, the EMA submitted an application from AstraZeneca and Oxford University for a conditional marketing authorization (CMA) for the COVID-19 vaccine, known as the COVID-19 AstraZeneca vaccine. The vaccine was also authorised by the regulatory authorities of Argentina, El Salvador, India, Mexico, Bangladesh, the Dominican Republic, Pakistan and Nepal for emergency use in their respective countries.

The vaccine is safe at refrigerator temperatures and costs between US$3 and US$4 per dose [76]. A tweet by the Belgian State Budget Secretary on 17 December announced that the European Union (EU) will pay EUR 1.78 (US$ 2.16) per dose [77]. According to AstraZeneca's Vice President of Operations and IT, Pam Cheng, by the end of 2020, the company will have about 200 million doses and capacity available worldwide. In addition to making 100 million doses available to the UK's NHS for its vaccine policy in June 2020 [78]. AstraZeneca and Emergent BioSolutions signed an agreement of US$87 million to produce vaccine doses specifically for the US market. The agreement was part of the Operation Warp Speed initiative of the Trump administration to develop and scale targeted vaccine production rapidly before the end of 2020 [79]. Catalent will be responsible for the process of finishing and packaging [80]. Most of the UK's manufacturing work will be done.

Initial purchases of 300 million doses from the company for low- to middle-income countries were made on 4 June 2020 by the World Health Organization (WHO) COVAX facility [81]. AstraZeneca and the Serum Institute of India (SII) also reached a licencing agreement to supply 1 billion doses of the Oxford University vaccine to middle and low-income countries, including India [82]. A grant from the Bill and Melinda Gates Foundation on 29 September 2020 allowed COVAX to secure an additional US$3 per dose of 100 million COVID-19 vaccine doses from either AstraZeneca or Novavax [83]. On 13 June 2020, AstraZeneca signed an agreement with the Inclusive Vaccines Alliance, a group formed by France, Germany, Italy and the Netherlands, to deliver up to 400 million doses to all European countries.

In August 2020, AstraZeneca decided to supply US$1.2 billion worth of 300 million doses to the US, meaning a cost of US$4 per dose. The funding also includes development and clinical trials, an AstraZeneca spokesperson said [85]. In September 2020, AstraZeneca agreed to supply Canada with 20 million doses [86]. Switzerland reached an agreement with AstraZeneca in October 2020 to pre-order up to 5.3 million doses [87]. Thailand ordered 26 million doses of AstraZeneca vaccine in November 2020 [88]. Two doses of vaccine per person are needed, so the ordered sum will only cover 13 million people [89]. In January 2021, the Prayut cabinet later authorised a budget for ordering 35 million additional doses [90] Siam Bioscience, a Vajiralongkorn-owned company, would obtain technical transfer for co-investment [91].

South Korea signed a deal with AstraZeneca in December 2020 to secure 20 million doses of its vaccine, with the first shipment scheduled to

commence in January 2021. The vaccine remained under consideration by the South Korean Disease Control and Prevention Agency as of January 2021 [92] On 7 January 2021, the South African government declared that the Serum Institute of India had received an initial 1 million doses, followed by another 500,000 doses in February [93] Myanmar signed a deal with the Serum Institute of India to procure 30 million doses in February. Myanmar will collect doses from February 2021 for 15 million persons [94].

ADVANCEMENT IN COVID-19 VACCINE

BBV154 - A novel adenovirus vectored, intranasal vaccine for COVID-19

An intranasal vaccine induces a broad immune response, neutralising the IgG, mucosal IgA, and T cell defences, the main attributes of BBV154. Immune responses at the infection site (in the nasal mucosa) are important for blocking both COVID-19 infection and transmission. Due to the nasal mucosa's coordinated immune systems, the nasal path has excellent capacity for vaccination. Needle-free, non-invasive. Ease of management-does not need health care staff who are educated. Removal of threats linked with needles (injuries and infections). High conformity (ideally appropriate for adults and children).Scalable production, capable of satisfying global demand. Protective efficacy in mice and hamsters of the candidate vaccine ChAd-SARS-CoV-2-S demonstrated.

Single-dose immunisation of ChAd-SARS-CoV-2-S in mice and hamsters offered superior safety against SARS-CoV-2 challenges, with more than one or two intramuscular immunizations with the same vaccine and dose. SARS-CoV-2 post-challenge viral clearance was found in both the lower and upper airways. Thus, ChAd-SARS-CoV-2-S intranasal immunisation will produce an immune response in the nose, which is the entry point for the virus, thus defending against illness, invasion, and transmission. [95]. (Fig: 1)

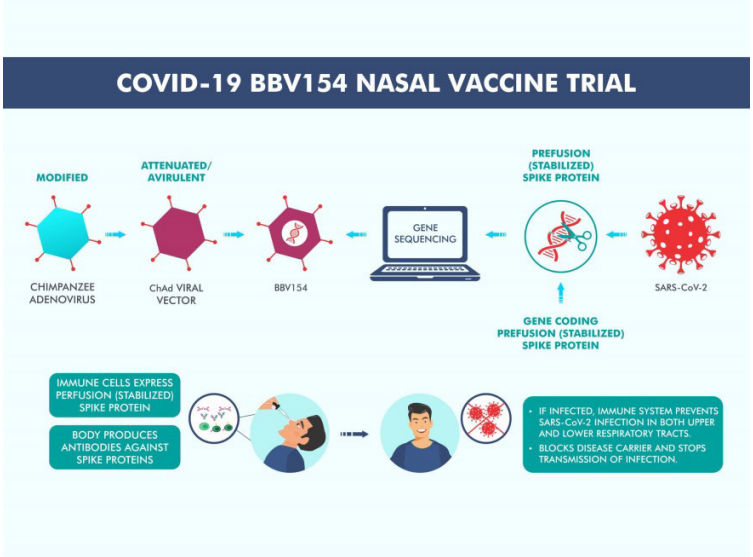

Fig 1: Covid-19 BV154 Nasal Vaccine Trial

CONCLUSION

The Corona virus (COVID-19) is circulating across the world at an unprecedented pace. The virus epidemic has confronted the commercial, medical and public health system of the world. Elderly and immuno compromised patients are also vulnerable to the lethal effects of the virus. There is actually no proven cure for the infection and, while some treatment protocols have been successful, there is no documented cure. Therefore, with the necessary preventive methods, the virus can be managed. The two Indian vaccines could assist in managing potential zoonotic outbreaks.

REFERENCES

[1]. Lu R, Zhao X, Li J, Genomic characterization and epidemiology of novel coronavirus: implications for virus origins and receptor binding. Lancet. https://doi.org/10.1016/S0140-6736 (20), 2020, 395: 564– 574, 30251-8

[2]. Chen N, Zhou M, Dong X, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 395(10223), 2020, 507– 513. https://doi.org/10.1016/S0140-6736.

[3]. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 579, 2020, 270– 273. https://doi.org/10.1038/s41586-020-2012-7

[4]. Backer J, Klinkenberg D, Wallinga J. Incubation period of novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, Euro Surveill, 2020, 25:2000062. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062

[5]. Desselberger U. Virus taxonomy: classification and nomenclature of viruses. Seventh report of the International Committee on Taxonomy of Viruses. In: van Regenmortel MHV, Fauquet CM, Bishop DHL, Carstens EB, Estes MK, Lemon SM, Maniloff J, Mayo MA, McGeoch DJ, Pringle CR, Wickner RB, eds. International Union of Microbiological Societies. San Diego: Virus Research, 2002, 1162.

[6]. AlNajjar N, Attar L, Farahat F, et al. Psycho behavioral responses to the 2014 Middle East respiratory syndrome-novel corona virus (MERS CoV) among adults in two shopping malls in Jeddah, western Saudi Arabia. Eastern Mediterranean Health Journal, 22, 2016, 817– 823.

[7]. Li J, Li JJ, Xie X, et al. Game consumption and the 2019 novel coronavirus. Lancet Infect Dis. 20, 2020, 275– 276. https://doi.org/10.1016/S1473-3099(20)30063-3

[8]. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/-ccov/types, 2020.

[9]. World Health Organization. Coronavirus disease (COVID-19) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019, 2020.

[10]. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. https://www.who.int/publications/i/item/10665-331501. Accessed, 2020.

[11]. World Health Organization. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus, 2019.

[12]. https://www.bharatbiotech.com/covaxin.html

[13]. https://www.indiatoday.in/coronavirus-outbreak/vaccine-updates/story/covaxin-approval-row-how-india-approves-vaccines-explained-1756049-2021-01-05.]

[14]. ICMR teams up with Bharat Biotech to develop Covid-19 vaccine". Livemint, 2020.

[15]. Chakrabarti A. "India to develop 'fully indigenous' Covid vaccine as ICMR partners with Bharat Biotech". ThePrint, 2020.

[16]. "India's First COVID-19 Vaccine Candidate Approved for Human Trials". The New York Times, 2020.

[17]. "Human clinical trials of potential Covid-19 vaccine 'COVAXIN' started at AIIMS". DD News. PrasarBharati, Ministry of I & B, Government of India, 2020.

[18]. Press, Associated. "Asia Today: Amid new surge, India tests potential vaccine". Washington Post. Retrieved, 2020.

[19]. "Delhi: 30-year-old is first to get dose of trial drug Covaxin". The Indian Express, 2020.

[20]. Ella, Raches; Mohan, Krishna; Jogdand, Harsh; Prasad, Sai; Reddy, Siddharth; Sarangi, Vamshi Krishna; Ganneru, Brunda; Sapkal, Gajanan; Yadav, Pragya; Panda, Samiran; Gupta, Nivedita; Reddy, Prabhakar; Verma, Savita; Rai, Sanjay; Singh, Chandramani; Redkar, Sagar; Gillurkar, Chandra Sekhar; Kushwaha, Jitendra Singh; Rao, Venkat; Mohapatra, Satyajit; Guleria, Randeep; Ella, Krishna; Bhargava, Balram"Safety and immunogenicity trial of an inactivated SARS-CoV-2 vaccine-BBV152: a phase 1, double-blind, randomised control trial". medRxiv, 2020. doi:10.1101/2020.12.11.20210419.

[21]. Perappadan, BinduShajan. "Coronavirus | Covaxin phase-1 trial results show promising results". The Hindu. Retrieved, 2020.

[22]. Sabarwal, Harshit. "Covaxin's phase 1 trial result shows robust immune response, mild adverse events". Hindustan Times. Retrieved, 2020.

[23]. "Coronavirus | Covaxin Phase III trial from November". The Hindu, 2020.
[24]. Ganneru B, Jogdand H, Daram VK, Molugu NR, Prasad SD, Kannappa SV, "Evaluation of Safety and Immunogenicity of an Adjuvanted, TH-1 Skewed, Whole Virion InactivatedSARS-CoV-2 Vaccine - BBV152", 2020. doi:10.1101/2020.09.09.285445.
[25]. "An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers". clinicaltrials.gov (Registry). United States National Library of Medicine. NCT04641481. Retrieved, 2020.
[26]. "Bharat Biotech begins Covaxin Phase III trials". The Indian Express, 2020.
[27]. Sen M. "List of states that have started phase 3 trials of India's first Covid vaccine". Mint, 2020.
[28]. "70%-80% Drop In Participation For Phase 3 Trials Of Covaxin: Official". NDTV, 2020.
[29]. "Bharat Biotech's Covaxin given conditional nod based on incomplete Phase 3 trial results data". The Print. 2021.
[30]. "Covaxin phase-3 trials to end today, average efficacy 60-70%". Deccan Herald, 2021.
[31]. Hoeksema F, Karpilow J, Luitjens A, Lagerwerf F, Havenga M, Groothuizen M, "Enhancing viral vaccine production using engineered knockout vero cell lines - A second look". Vaccine. 36 (16), 2018, 2093–2103. doi:10.1016/j.vaccine.2018.03.010. PMID 29555218.
[32]. "Coronavirus vaccine update: Bharat Biotech's Covaxin launch likely in Q2, no word on pricing yet". www.businesstoday.in. India Today Group. Retrieved, 2020.
[33]. "Odisha fast tracks coronavirus vaccine manufacturing unit". The New Indian Express, 2020.
[34]. Raghavan P. "Bharat Biotech exploring global tie-ups for Covaxin manufacturing". The Indian Express, 2020.
[35]. Reuters Staff. "Ocugen to co-develop Bharat Biotech's COVID-19 vaccine candidate for U.S." Reuters. Retrieved 2021.
[36]. "Bharat Biotech, Ocugen to co-develop Covaxin for US market". The Economic Times. Retrieved 2021.
[37]. "Bharat Biotech inks pact with Precisa Med to supply Covaxin to Brazil". mint. 2021.
[38]. Ghosh N. "Bharat Biotech seeks emergency use authorization for Covid-19 vaccine". Hindustan Times, 2020.
[39]. "Coronavirus | After SII, Bharat Biotech seeks DCGI approval for Covaxin". The Hindu. 2020.
[40]. "Expert panel recommends granting approval for restricted emergency use of Bharat Biotech's Covaxin". The Indian Express, 2021.
[41]. "Coronavirus: India approves vaccines from Bharat Biotech and Oxford/AstraZeneca". BBC News. Retrieved 2021.
[42]. "Disputes Mount, but Heedless Govt Intent on Rolling Vaccine Candidates Out". The Wire, 2021.
[43]. https://www.livemint.com/ Retrieved, 2021.
[44]. https://indianexpress.com/article/explained/covid-vaccine-back-up-bharat-biotech-aiims-icmr-7131586/.
[45]. O'Reilly P, "A Phase III study to investigate a vaccine against COVID-19". ISRCTN (Registry), 2020. Doi: 10.1186/ISRCTN89951424. ISRCTN89951424.
[46]. "COVID-19 Vaccine Trials | COVID-19". covid19 vaccinetrial.co.uk., 2020.
[47]. "Oxford team to begin novel coronavirus vaccine research". University of Oxford. Retrieved 2020.
[48]. Callaway E. "Why Oxford's positive COVID vaccine results are puzzling scientists". Nature. 588 (7836), 2020, 16–18. doi:10.1038/d41586-020-03326-w. PMID 33230278. S2CID 227156970.
[49]. "Covid-19: Oxford-AstraZeneca coronavirus vaccine approved for use in UK". BBC News. BBC. Retrieved 2020.
[50]. "Covid: Brian Pinker, 82, first to get Oxford-AstraZeneca vaccine". BBC News. BBC, Retrieved 2021.
[51]. Arashkia A, Jalilvand S, Mohajel N, Afchangi A, Azadmanesh K, Salehi-Vaziri M, "Severe acute respiratory syndrome-coronavirus-2 spike (S) protein based vaccine candidates: State of the art and future prospects". Reviews in Medical Virology. n/a (n/a): e2183, 202. doi:10.1002/rmv.2183. PMC 7646037.
[52]. "Exeter Fellow Dr Catherine Green leads the production of a potential COVID-19 vaccine in Oxford". Exeter College, 2020. Retrieved 2020.
[53]. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, Jiang C "SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway". Cell Research. 18(2), 2008, 290–301. doi:10.1038/cr.2008.15. PMC 7091891. PMID 18227861.

[54]. "AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19". AstraZeneca (Press release). Retrieved 2020.
[55]. "Oxford team to begin novel coronavirus vaccine research". University of Oxford. Retrieved 2021.
[56]. Coleman J (10 June 2020). "Final testing stage for potential coronavirus vaccine set to begin in July". TheHill. Retrieved 2020.
[57]. "AZN, IQV Team Up To Accelerate COVID-19 Vaccine Work, RIGL's ITP Drug Repurposed, IMV On Watch". RTTNews. Retrieved 2020.
[58]. "Phase 3 Clinical Testing in the US of AstraZeneca COVID-19 Vaccine Candidate Begins". National Institutes of Health (NIH). Retrieved 2020.
[59]. Wu KJ, Thomas K. "AstraZeneca Pauses Vaccine Trial for Safety Review". The New York Times. ISSN 0362-4331. Retrieved 2020.
[60]. Loftus P. "AstraZeneca Covid-19 Vaccine Trials Resume in U.K." Wall Street Journal. ISSN 0099-9660. Retrieved 2020.
[61]. Grady D, Wu KJ, LaFraniere S (19 September 2020). "AstraZeneca, Under Fire for Vaccine Safety, Releases Trial Blueprints". The New York Times. ISSN 0362-4331. Retrieved 2020.
[62]. "AstraZeneca resumes vaccine trial in talks with US". Japan Today, 2020.
[63]. "FDA authorises restart of the COVID-19 AZD1222 vaccine US Phase III trial". AstraZeneca (Press release). Retrieved, 2020.
[64]. Reuters Staff. "U.S. health secretary says AstraZeneca trial in United States remains on hold: CNBC". Reuters. Retrieved 2020.
[65]. Voluntáriobrasileiroqueparticipava dos testes da vacina de Oxford e morreu com a Covid era médico e ex-aluno da UFRJ, Globo
[66]. Simões E, Burger L. "AstraZeneca COVID-19 vaccine trial Brazil volunteer dies, trial to continue". Reuters. Retrieved 2020.
[67]. "Oxford University breakthrough on global COVID-19 vaccine". University of Oxford, 2021.
[68]. Robbins, Rebecca; Mueller, Benjamin, "After Admitting Mistake, AstraZeneca Faces Difficult Questions about Its Vaccine". The New York Times. ISSN 0362-4331. Retrieved 2020.
[69]. Boseley, Sarah "Oxford/AstraZeneca vaccine to undergo new global trial". the Guardian. Retrieved 2020.
[70]. "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK - The Lancet". Retrieved 2020. This article incorporates text by Voysey. available under the CC BY 4.0 license.
[71]. "Covid: Trials to test combination of Oxford and Sputnik vaccines". BBC News. Retrieved 2020.
[72]. "Oxford vaccine researchers have found 'winning formula', AstraZeneca chief says". The Independent. Retrieved 2020.
[73]. "Government asks regulator to approve supply of Oxford/AstraZeneca vaccine". GOV.UK. Department of Health and Social Care. Retrieved 2020.
[74]. "Oxford University/AstraZeneca vaccine authorized by UK medicines regulator". Gov.uk. Department of Health and Social Care. Retrieved 2020.
[75]. "AstraZeneca vaccine not ready for quick European approval, watchdog official says". www.reuters.com. Reuters. Retrieved 2020.
[76]. Belluz J. "Why the AstraZeneca-Oxford Covid-19 vaccine is different". Vox. Retrieved 2020.
[77]. Stevis-Gridneff, Matina; Sanger-Katz, Margot; Weiland, Noah."A European Official Reveals a Secret: The U.S. Is Paying More for Coronavirus Vaccines". The New York Times. Retrieved 2020.
[78]. "AstraZeneca to begin making vaccine". BBC. Retrieved 2020.
[79]. "AstraZeneca, Emergent BioSolutions sign $87M deal to produce U.S. supply of COVID-19 vaccine". FiercePharma. Retrieved 2020.
[80]. "AstraZeneca taps Catalent for COVID-19 vaccine finishing, packaging at Italian plant". FiercePharma. Retrieved 2020.
[81]. So, Anthony D; Woo, Joshua, "Reserving coronavirus disease, vaccines for global access: cross sectional analysis". BMJ: 3. doi:10.1136/bmj.m4750. ISSN 1756-1833. cited"Agreements with CEPI and Gavi and the

Serum Institute of India will bring vaccine to low and middle-income countries and beyond". AstraZeneca 2020.
[82]. Rajagopal, Divya, "AstraZeneca & Serum Institute of India sign licensing deal for 1 billion doses of Oxford vaccine". The Economic Times, 2020.
[83]. So & Woo (2020), p. 3 cited "New collaboration makes further 100 million doses of COVID-19 vaccine available to low- and middle- income countries". Gavi, the Vaccine Alliance, 2020.
[84]. "Covid-19: France, Italy, Germany and Netherlands sign vaccine deal for Europe". France 24, Retrieved 2020.
[85]. Roland D, "U.S. to Invest $1.2 Billion to Secure Potential Coronavirus Vaccine From AstraZeneca, Oxford University". Wall Street Journal. ISSN 0099-9660. Retrieved 2020.
[86]. https://www.cbc.ca/news/politics/covid19-briefing-trudeau-tam-1.5738503
[87]. Swiss sign next vaccine agreement with AstraZeneca". SWI swissinfo.ch. Retrieved 2020.
[88]. "เรื่องน่ารู้ของวัคซีนโควิด-19 ที่ไทยสั่งซื้อ". BBC ไทย (in Thai). Retrieved 2021.
[89]. "ทำความรู้จักออกซ์ฟอร์ด-แอสทราเซเนกาวัคซีนที่ไทยเลือก". มติชนออนไลน์ (in Thai). Retrieved 2021.
[90]. "ครม.ไฟเขียวงบซื้อวัคซีนโควิดเพิ่ม35ล้านโดสฉีดให้คนไทย66ล้าน". โพสต์ทูเดย์ (in Thai). Retrieved 2021.
[91]. "นายกฯสำนึกในพระมหากรุณาธิคุณร.10 ทรงให้"สยามไบโอไซเอนซ์"รองรับวัคซีนโควิด-19". BBC ไทย (in Thai). Retrieved 2021.
[92]. Shin, Hyonhee (3 December 2020). "South Korea reaches deal to buy AstraZeneca's COVID-19 vaccine candidate: media". Reuters. Retrieved 2021.
[93]. Felix, Jason. "SA will get 1 million doses of Covid-19 vaccine from India this month". News24.com. Retrieved 2021.
[94]. "Myanmar will get doses for 15 million people this February". 7day.news. Retrieved 2021.
[95]. https://www.bharatbiotech.com/intranasal-vaccine.html.

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